Manipulating the Microbiome to Treat Recurrent C. Diff

Novel Biotherapeutics

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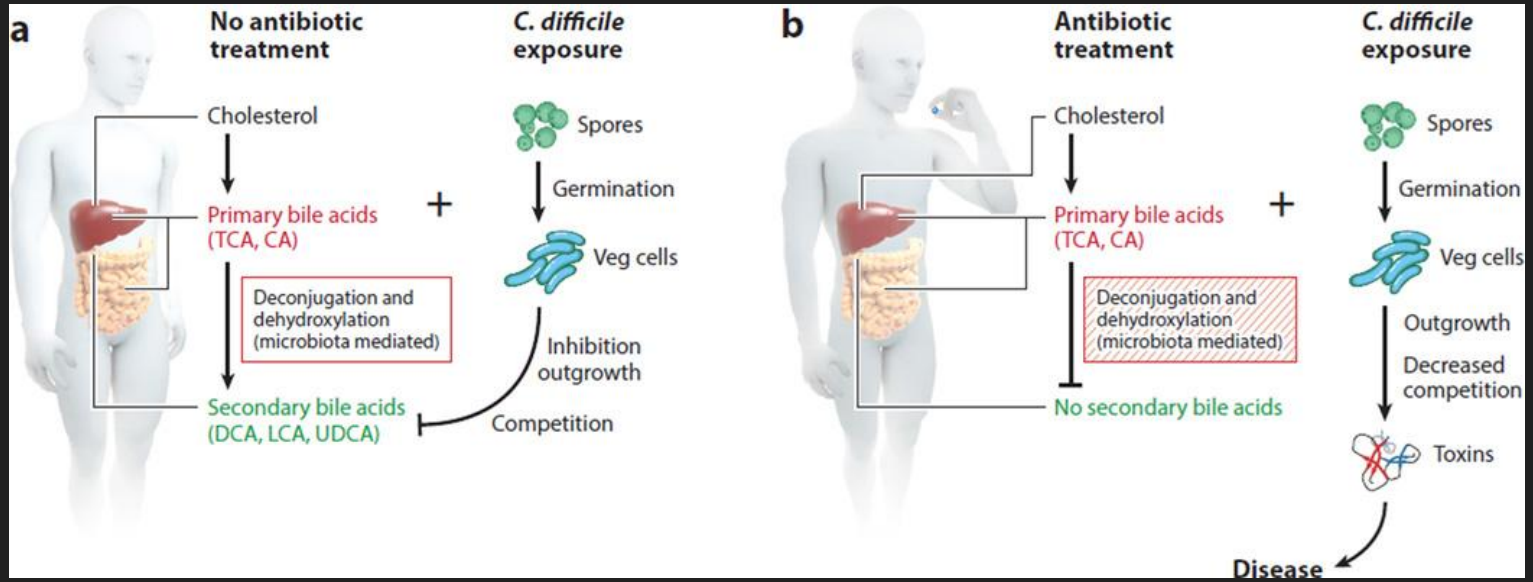
Outline

- The role of the microbiome in C. difficile infection
- Fecal microbiota transplant (FMT) and live biotherapeutic products (LBP)
- Probiotics and C. diff prevention?

Pathophysiology



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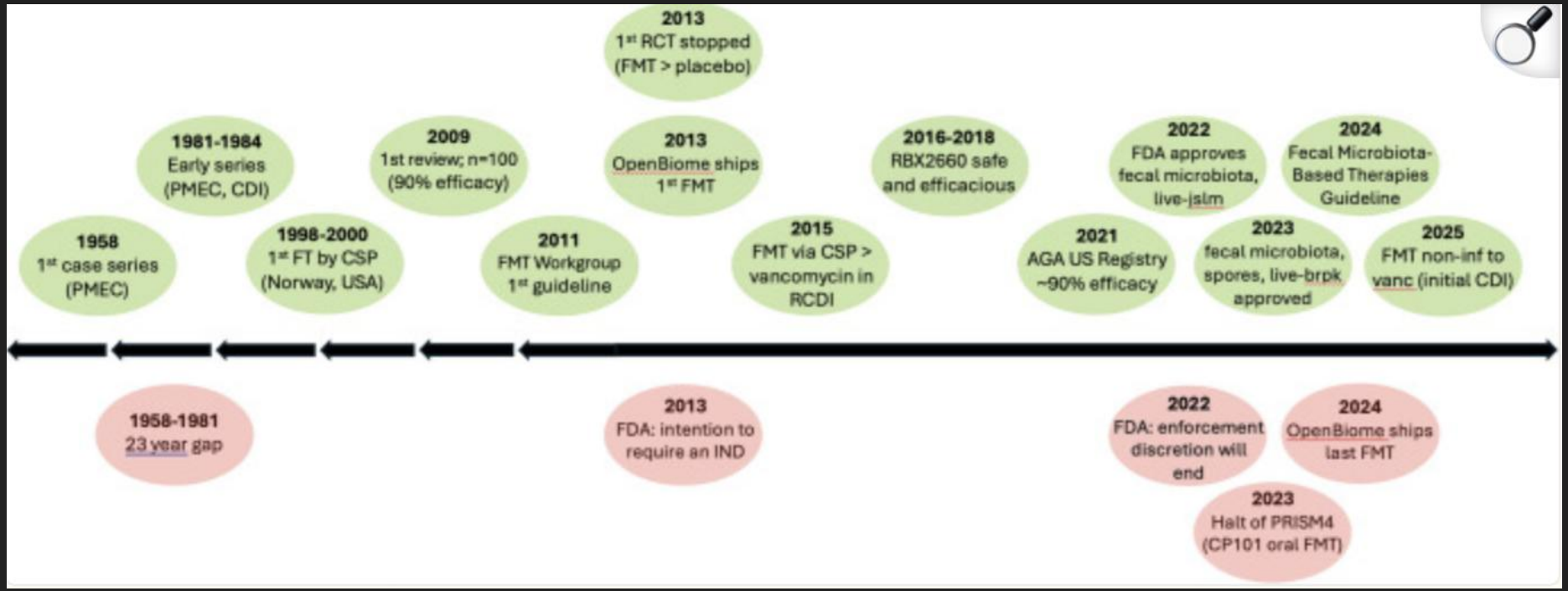
Therapeutic Options

- Traditional FMT-multiple modes of delivery, PO or colonoscopy preferred
- Rebyota (fecal microbiota, live-jslm; RBX2660)-enema
- VOWST (fecal microbiota spores, live-brpk, SER-109,)-capsules

FMT



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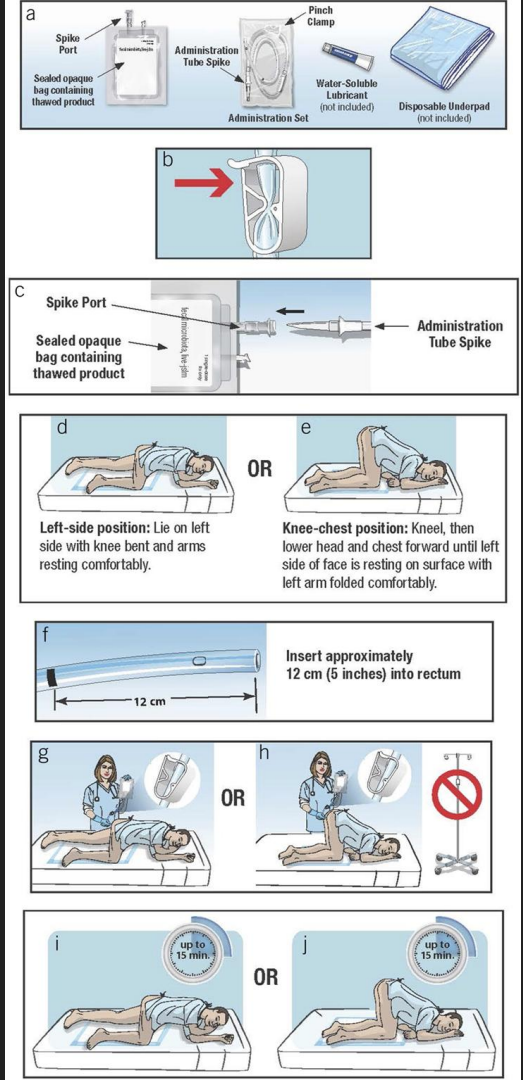
Rebyota

- Each dose from single, traceable donor
- After first recurrence of c. diff
- After completion of antibiotics with 24-72 hr washout
- Patients with IBD were included in open-label trial
- Contraindicated in severe neutropenia
- Off-label in fulminant c. diff



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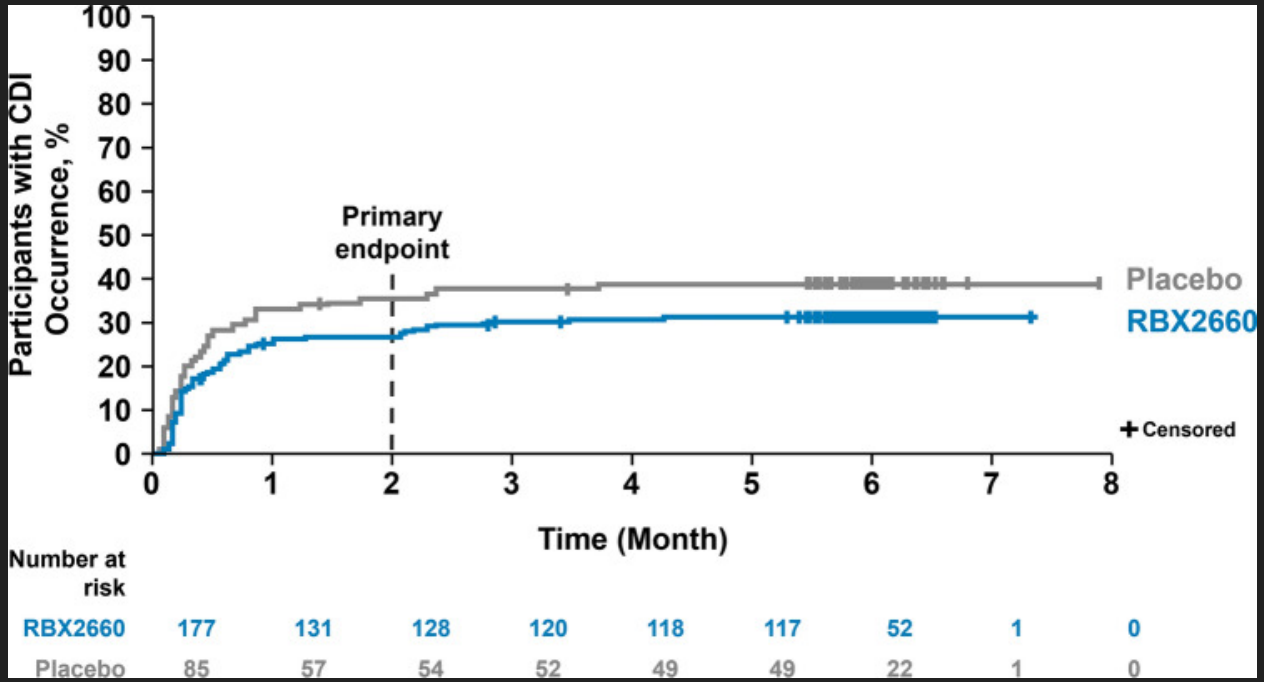
Kelly, Colleen R. MD, AGAF, FACG1; Fischer, Monika MD, MSc, AGAF, FACG2; Allegretti, Jessica R. MD, MPH, FACG3; LaPlante, Kerry PharmD, FCCP, FIDSA4; Stewart, David B. MD, FACS, FASCRS5; Limketkai, Berkeley N. MD, PhD, FACG (GRADE Methodologist)6; Stollman, Neil H. MD, FACG7. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. The American Journal of Gastroenterology 116(6):p 1124-1147, June 2021. | DOI: 10.14309/ajg.0000000000001278

PUNCH CD3



Khanna S, Assi M, Lee C, Yoho D, Louie T, Knapple W, Aguilar H, Garcia-Diaz J, Wang GP, Berry SM, Marion J, Su X, Braun T, Bancke L, Feuerstadt P. Efficacy and Safety of RBX2660 in PUNCH CD3, a Phase III, Randomized, Double-Blind, Placebo-Controlled Trial with a Bayesian Primary Analysis for the Prevention of Recurrent Clostridioides difficile Infection. Drugs. 2022 Oct;82(15):1527-1538. doi: 10.1007/s40265-022-01797-x. Epub 2022 Oct 26. Erratum in: Drugs. 2022 Oct;82(15):1539. doi: 10.1007/s40265-022-01805-0. PMID: 36287379; PMCID: PMC9607700.

PUNCH CD3

- >90% who achieved treatment success at 8 weeks had **sustained response** at 6 months (RBX2660 and placebo)
- In post hoc analysis of those with **first recurrence**, probability of treatment success was 88% with RBX2660 and 60% with placebo
- Success with second treatment:
  - 24 failed placebo -> 62.5% with treatment success within 8 weeks -> 100% sustained @ 6 months
  - 41 failed RBX2660 -> 53.7% treatment success at 8 weeks -> 86% sustained response

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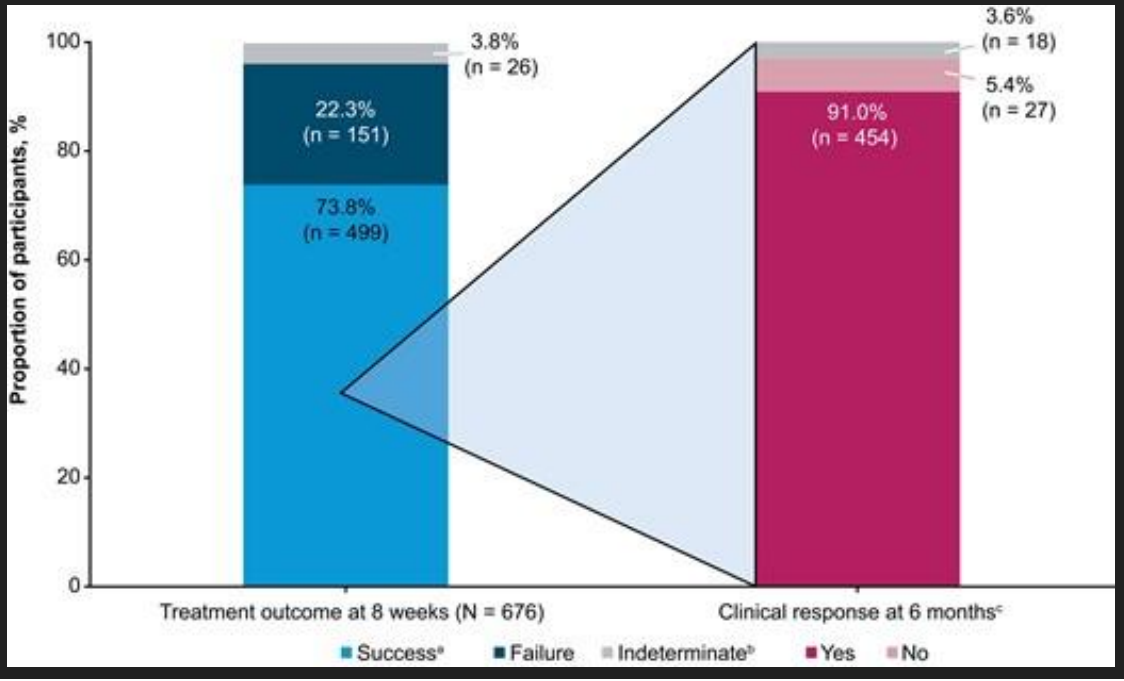
PUNCH CD3: OLS



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PUNCH CD3: OLS

Table 1.
Baseline Demographics, Characteristics, and Disposition (Safety Population)

Characteristic	RBL (N = 697)
Age ≥65 y	338 (48.5)
Sex, female	487 (69.9)
Race, White	654 (93.8)
No. of previous CDI episodes[a,b]	
2	186 (26.7)
3	268 (38.5)
≥4	239 (34.3)
Enrolling diagnostic test[c]	
PCR	432 (62.0)
EIA	75 (10.8)
GDH	50 (7.2)
Other[d]	65 (9.3)
Most recent antibiotic received	
Vancomycin	590 (84.6)
Fidaxomicin	99 (14.2)
Rifaximin	7 (1.0)

Charlson Comorbidity Index	
<3	329 (47.2)
≥3	368 (52.8)
GI comorbidities	
Ulcerative colitis	45 (6.5)
Crohn's disease	25 (3.6)
IBD (unspecified)[e]	4 (0.6)
IBS	97 (13.9)
GERD	288 (41.3)
Renal and urinary comorbidities	
CKD	74 (10.6)
Chronic urinary tract infections	61 (8.8)
Mild-to-moderate immunocompromising conditions[f]	
Malignant tumors	42 (6.0)
Other medical history[g]	19 (2.7)
Concomitant immunocompromising medications[f,h]	
Corticosteroids	23 (3.3)
Noncorticosteroids	92 (13.2)

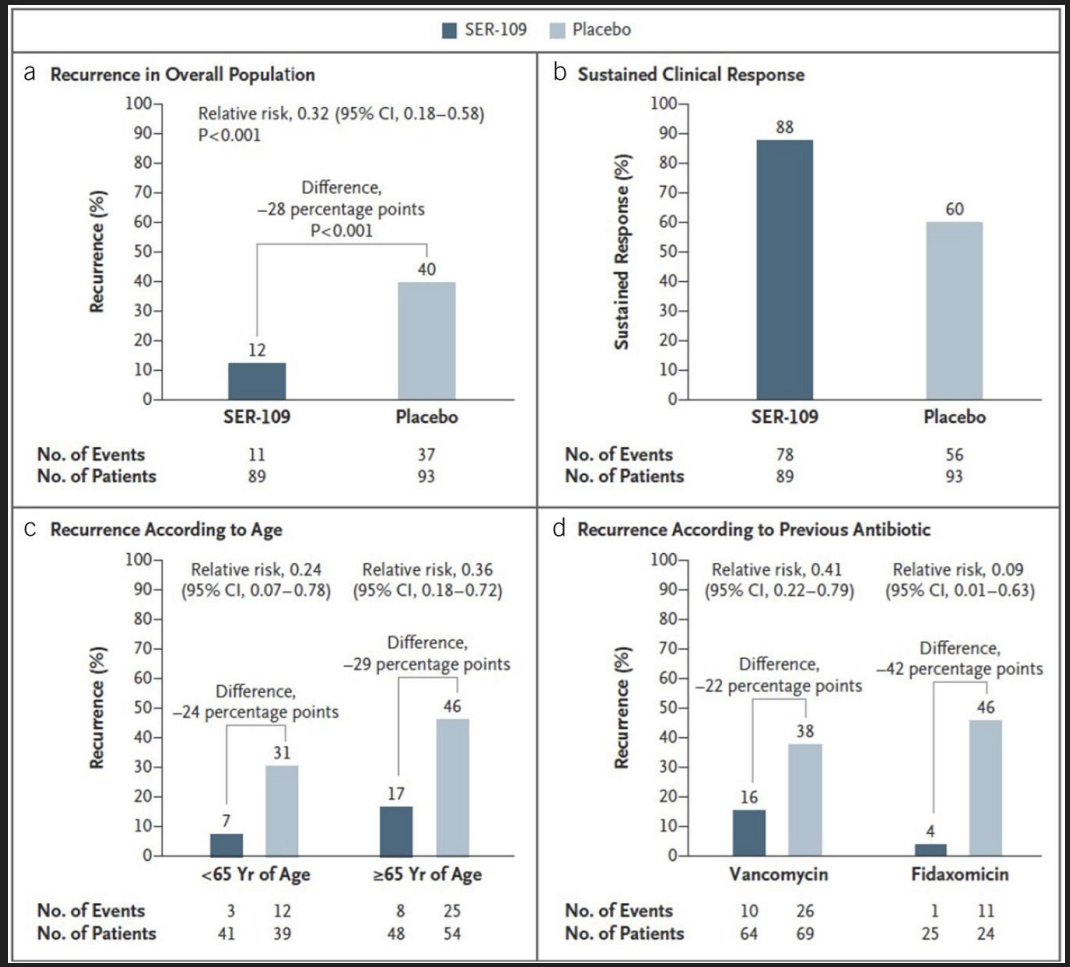
PUNCH CD3: OLS

Adverse Event	Within 8 Weeks (N = 697)	8 Weeks to 6 Months (N = 697)
	Events/Participants (% of Participants)	
Gastrointestinal disorders	411/205 (29.4)	82/51 (7.3)
Diarrhea	95/85 (12.2)	21/19 (2.7)
Abdominal pain	78/70 (10.0)	10/10 (1.4)
Nausea	44/41 (5.9)	5/5 (0.7)
Abdominal distension	46/38 (5.5)	2/2 (0.3)
Infections[a]	78/71 (10.2)	86/68 (9.8)
General disorders[b]	44/36 (5.2)	10/8 (1.1)
Investigations[c]	49/35 (5.0)	5/5 (0.7)

Vowst

- Isolated Firmicutes spores from single donor
- Capsule formulation, 4 capsules daily 3 days, 2-4 days after completing antibiotics
    - Clean out with 10 ounces of Magnesium citrate day prior or 8 hours prior after 8 hour fast
- Approved for recurrent c. diff (2+ total episodes)

ECOSPOR III



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ECOSPOR IV

- Patients whole failed placebo in Ecospor III (29) and group recruited for open label study (234)
- Patients with IBD remain excluded
- Added in those with first recurrence: 6.5% recurrence rate after treatment
- Overall recurrence rates were 8.7% at 8 weeks with 13.7% recurring at 24 weeks
- Similar safety to Ecospor III with GI symptoms but without serious adverse events

Sims MD, Khanna S, Feuerstadt P, et al. Safety and Tolerability of SER-109 as an Investigational Microbiome Therapeutic in Adults With Recurrent *Clostridioides difficile* Infection: A Phase 3, Open-Label, Single-Arm Trial. *JAMA Netw Open.* 2023;6(2):e2255758. doi:10.1001/jamanetworkopen.2022.55758

Aside on Probiotics

- ACG recommends against probiotics for prevention of primary and recurrent C. difficile
- AGA conditionally recommends certain strains of probiotics to prevent recurrence of c. difficile
- PLACIDE trial: no benefit of probiotics in preventing antibiotic associated CDI
- Overall, not recommended

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AGA Guidelines

- Prevention with fecal microbiota–based therapies can be considered in patients after the second recurrence (third episode) of CDI or in select patients at high risk of either recurrent CDI or a morbid CDI recurrence.
- In mildly or moderately immunocompromised adults with recurrent *C difficile* infection, the AGA suggests the use of conventional fecal microbiota transplant upon completion of standard of care antibiotics over no fecal microbiota transplant. *Insufficient data to recommend fecal microbiota spores live-brpk or fecal microbiota live-jslm*
- In severely immunocompromised adults with recurrent *C difficile* infection, the AGA suggests against the use of fecal microbiota–based therapies
- **In adults hospitalized with severe or fulminant *C difficile* infection not responding to antimicrobial therapy, the AGA suggests the use of conventional fecal microbiota transplant over no fecal microbiota transplant**

AGA Clinical Practice Guideline on Fecal Microbiota–Based Therapies for Select Gastrointestinal Diseases
AGA Clinical Guidelines Committee et al.
Gastroenterology, Volume 166, Issue 3, 409 - 434

ACG Guidelines

- We recommend patients experiencing their second or further recurrence of CDI be treated with FMT
- We suggest FMT be considered for patients with severe and fulminant CDI refractory to antibiotic therapy, in particular, when patients are deemed poor surgical candidates
- We recommend FMT be delivered through colonoscopy or capsules for treatment of rCDI
- We suggest repeat FMT for patients experiencing a recurrence of CDI within 8 weeks of an initial FMT
- Recommend “considering” FMT for patients with IBD and recurrent c. diff

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Take Home Points

- Traditional FMT is difficult to obtain
- Consider VOWST or Rebyota after second recurrence of C. diff (and maybe after first recurrence, better data for Rebyota)
- Data for Rebyota > VOWST for recurrent C. diff in IBD
- How to order: search “VOWST” or “Rebyota” in orders in Epic